EXPERIMENTS

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PHYSIOLOGICAL ACTION OF BROMIDE OF POTASSIUM AND AMMONIUM

(As determined on Man and the Lower Animals).

By ROBERT AMORY, M.D.

Selected Paper read before the Massachusetts Medical Society, June 1, 1869.

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THE PHYSIOLOGICAL ACTION OF BROMIDE OF POTASSIUM AND AMMONIUM.

CHAPTER I.

BROMIDE OF POTASSIUM is absorbed readily by the mucous membrane of the mouth. This proposition would be illustrated by the following experiments:

EXP. I.—Under the effects of ether, a dog was operated upon for ligature of the œsophagus. When this had been accomplished, a solution containing 160 grains of this salt was placed in the mouth of the animal. In ten minutes after the contact of the drug with the buccal mucous membrane, blood ʒ j. was drawn from the carotid artery, and, examined by means of chlorinated water and bisulphide of carbon, gave the peculiar reaction of the liberation of bromine, viz., a reddish yellow color.

The bromide could only have been absorbed by the mucous membrane of the mouth and pharynx, for great care was taken to prevent the contact of the solution with any other tissue.

EXP. II.—A strong solution of this same salt was retained in the mouth for five minutes and then thoroughly ejected; the mouth was carefully rinsed out with fresh water, and wiped dry and again rinsed. As the solution was kept in the anterior portion, and by the tongue prevented from touching the pharynx, there could now have been no possibility of the presence of the salt in the mouth.

The examination of 25 cubic centimetres of urine, passed

two hours and a half afterwards, indicated the presence of a large amount of the bromide.

In these and other experiments not here related the bromide was present in the blood of dogs and in the urine of man, to whom the drug had been administered by means of the mucous membrane of the mouth only, and it is thus proved that bromide of potassium can readily be absorbed by this portion of the mucous membrane. There is no doubt but that the absorption is rapidly accomplished. This is shown in these two experiments and by the following—

Exp. III.—Ten grs. in an aqueous solution were introduced by an œsophagean tube into the stomach of a rabbit. Six minutes after, ʒ iss. of blood was taken from the carotid artery, was carefully analyzed* and found to contain, by calculation, from the amount of bromine obtained, three and three-fifths milligrammes (or $\frac{9}{1000}$ of a grain) of bromide of potassium. We supposed the weight of the rabbit to be 6 lbs. or 5250 grains; from an easy calculation, the inference seems reasonable that, if there was as much of this salt in the rest of the blood as in this specimen, we had recovered about one third of the whole quantity given. Considering that in an analysis of thirty-five centigrammes of bromide of potassium which had been previously dissolved in an ounce of urine, one-tenth part was not recovered in the process, we could suppose that more of the salt might have been recovered in the above named experiment than we actually obtained. In six minutes, therefore, a large portion of the drug was absorbed. Compare this with an experiment made upon man—

Exp. IV.—Eight grains of the salt were swallowed, and the mouth carefully rinsed out with water and wiped several times. Five minutes after, ʒ ij. of saliva were collected,

* To prevent weariness, the details of this analysis will be reserved for another portion of this paper.

which, analyzed qualitatively, was found to contain a large amount of a bromide from the intense brownish yellow tinge, given to bisulphide of carbon by the addition of two or three drops of strong chlorine water. In another experiment a *slight* indication of the presence of a bromide occurred in urine collected twenty minutes after the ingestion of twenty grains.

Exp. V.—Some blood, drawn from the carotid artery of a rabbit ten minutes after the exhibition of 10 grs. by the stomach tube, failed to show the presence of any free bromine. By adding, however, the chlorine water, a bromide was decomposed, liberating the bromine.

Exp. VI.—The body of the experimenter was immersed for fifteen minutes in a warm bath (96° Fah.), containing an ounce and a quarter of bromide of potassium to 20 gallons of water. The urine passed during the night and following morning was retained, and then a portion carefully tested for a bromide. No indication of its presence was discovered. In this case no eruption of the skin occurred, showing that prolonged contact of the drug does not irritate the skin.

Exp. VII.—At another time about ʒ ij. of this salt was dissolved in a foot-tub containing five gallons of water. The feet and ankles were then immersed for 18 minutes, the temperature of the water being kept at about 72° Fah.

The urine passed three hours after showed, by the usual test, that a salt of bromine was present in it. It is needless to state that no bromide had been taken for four weeks previous to this experiment.

Supplementary Exp. (*a*).—Thinking that the results of these two experiments might be doubted, they both were repeated under somewhat different conditions. I asked my friend Dr. ——— to dissolve ℥ x. of br. of pot. in xx. galls. of water at a temperature above 98° F. He informed me that there was not quite enough water to cover his whole

body, which was kept immersed for 12 minutes, the temperature of the solution varying from 108° to 102° F.; he afterwards washed the body with fresh water, and then wiped it dry. He reported that he felt more languid than usual after a hot bath (the temperature of the water was very high), and imagined that he experienced a saline taste half an hour after the bath. I carefully analyzed his urine (℥ v.) passed during 12 hours after the bath, but could not find the *least* trace of a bromide.

I was prevented from performing this last experiment, because I had, two days before, taken a foot-bath of a solution of this drug, followed the next morning by a cold sponge bath containing ℥ ij. of the bromide to a pail of water. ℥ iv. of urine passed during that day gave a very decided reaction of a salt of bromine. Thus by a warm bath no bromide had been eliminated nor absorbed; while after a cold bath its presence in the urine proved its absorption by the skin. This agrees fully with the statement quoted by Dr. Stillé,* that in a warm bath at 96° F. the body exhales, and at a temperature below 80° the body imbibes moisture.

This drug can be absorbed also by the rectum; for, in the following experiment—

Exp. VIII.—A rectal injection of beef tea, containing an ordinary dose of bromide of potassium, was given to a patient and the urine passed during the next 18 hours collected. ℥ ij. of this gave a decided reaction of a salt of bromine. This, and other experiments since undertaken, prove that the rectum will absorb this drug, when dissolved in a vehicle which will prevent its irritating properties from manifesting themselves. When given in warm water by the rectum, a violent irritation is induced, with a tendency to diarrhœa and tenesmus.

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* Mat. Med. and Therapeutics, vol. i. p. 52.

PROP. A.—These and other experiments, not here related, prove that bromide of potassium is absorbed readily and rapidly by the mucous membrane, generally, and that it is not readily absorbed by the skin except at a temperature below that of blood heat.

Is bromide of potassium decomposed in the system, and may a chemical transformation explain its method of action?

Dr. Bill, in a late number of the American Journal of Medical Sciences, proposes that there may be a chemical interchange *in the blood* between chloride of sodium and bromide of potassium, and says that when bromide of potassium meets chloride of sodium, chloride of potassium and bromide of sodium result, that is, outside of the body. He also states, that as there is an excess of chlorides eliminated after the use of this drug, perhaps its action may be explained by there being a diminution of the chlorides in the blood. I have taken considerable trouble to determine the correctness of this theory, and can find no other authority for this chemical reaction, and cannot see how such a theory can be proved by the known methods of chemistry.

His argument is based upon the fact that there is an increase in the amount of chlorides eliminated by the urine after the ingestion of the bromide in doses less than what may endanger life. He tabulates a report of the quantity of chloride of silver obtained from the urine of a person taking daily doses of the bromide; and, also, finds an increase in the amount of potassium eliminated by the kidneys. He does not, according to this table, separate the bromide of silver from the chloride of silver.

Consequently an increased amount of the mixed bromide and chloride of silver (which are thrown down together by nitrate of silver), found in the urine after the use of this drug, proves no more than that the bromides and chlorides are eliminated together in the urine. In some analyses

which were conducted under my supervision by Mr. Wood of the present medical class, it was found that this increase in amount of the nitrate of silver *ppt.* was due to the union of bromine and chlorine with the silver; and the bromine was then separated, leaving, I should judge, only the normal amount of chlorine behind.

In our experiments the proportion of bromine to chlorine eliminated was as 2:1.

Another refutation of this theory might be adduced from the fact, that bromide of sodium *never* produces a physiological action which is similar to that produced by the bromide of potassium.

CHAPTER II.

CHEMICAL PROPERTIES OF BROMIDE OF POTASSIUM.

It would be in place here to mention some of the chemical properties of bromide of potassium, and especially in detail the process by which our investigations were conducted.

This is a very fixed salt, losing no weight by fusion at a red heat. The stronger acids with difficulty liberate the bromine at an ordinary temperature. Potassium has a stronger affinity for chlorine than for bromine, and a stronger affinity for bromine than for iodine. If to a solution of bromide of potassium a drop or two of strong chlorine water be added, the bromine is set free in the liquid, and ether, chloroform, or bisulphide of carbon will absorb the gas, producing a strong brownish red tinge to either. The bisulphide of carbon we found of the most advantage in this process.

This is a very delicate test, M. Rabuteau* having discov-

* Gazette Hebdomadaire, April 24th, 1868.

ered an absurdly small quantity; the only objections to this method being that the organic matters in the urine interfere with its reaction, and that an alkaline fluid may also prevent the decomposition. To overcome these difficulties, we evaporated the urine to dryness, and then ignited the residue, keeping it at a red heat for about half an hour. Then to the solution a drop or two of nitric acid was added, until blue litmus paper was changed to red. Then the chlorine water was added, drop by drop, until the peculiar reddish color was visible. This color was intensified by the addition of two or three drops of the bisulphide of carbon, which, on agitation, absorbed all the bromine. Too much chlorine forms a white precipitate, chloride of bromine; therefore caution is required in adding the chlorine water. Sometimes in the decomposition of the organic matters the bromine escapes, so that the addition of a small fragment of pure soda or potassa may be placed in the urine to take up the bromine*. M. Rabuteau prefers the soda to potassa, because the former is more easily decomposed by nitric acid and chlorine. This was our test for the presence of a bromide.

The process for calculating the amount of a bromide present may be best described by giving a detailed account of *one* experiment—

Exp. IX.—Thirty-five centigrammes of bromide of potassium was dissolved in an ounce (21 grammes) of urine. The urine was evaporated to dryness, charred and ignited. The residue was then treated with boiling water and filtered from the carbon. But little of the coloring matter of the urine was present in the filtrate. Nitrate of silver was then added in excess, and the mixture allowed to stand twenty-four hours. The precipitate was washed thoroughly with

* Op. cit.

boiling water, acidulated with a few drops of nitric acid. This precipitate consisted of a mixture of the bromide and chloride of silver, with some of the coloring matters of the urine. To free the latter, an excess of ammonia was added to dissolve the mixed bromide and chloride, leaving the coloring matters behind. The residue was washed with water. The filtrate was acidulated with nitric acid, and bromide and chloride of silver again precipitated. This precipitate was then washed with acidulated water as before. The filter paper had previously been dried and weight ascertained. This, after being dried, was now weighed with its precipitate and found to have increased to the amount of 6.075 grammes. Of this a portion was placed in a crucible, the weight of which had been previously ascertained.

The weight of crucible without contents was	6.705 grms.
The weight of crucible with contents was	7.025 grms.
Thus the bromide and chloride of silver weighed	.320 grms.

This portion was then fused in the crucible, and chlorine gas, washed in sulphuric acid, was passed over by means of a porcelain tube fitting into the platinum cover of the crucible. The chlorine displaces the bromine which is set free (this process must be continued till the crucible ceases to lose weight). From the loss in weight the amount of bromine may be calculated from the following proportion:*

1. "The difference between the equivalents of chlorine and bromine: the equivalent of bromine = the loss of weight: ×." Thus 44.54:80 = loss of weight: ×.

From the amount of bromine originally in the crucible may be calculated the amount of bromine in the whole precipitate as follows:

* Quantitative Chem. Anal. Fresenius, by Bullock & Vacher, p. 446.

2. Weight of the whole mixed precipitate: weight of that in the crucible = × (bromine in the whole): bromine in the crucible.

From the amount of bromine in the whole mixed precipitate, the amount of bromide of potassium recovered may be determined thus:

3. Equivalent of bromine: equivalent of bromide of potassium = weight of bromine found in the mixed precipitate: × (or bromide of potash).

From these three problems the result of the preceding experiment was obtained. It was supposed that the bromine discovered in this process was united with potassium which was found in the urine. The method of obtaining the amount of this is so difficult and protracted that we are contented with Dr. Bill's* statement, that in his experiments the potash was increased "fourfold" in the urine, when bromide of potassium was taken.

The result obtained was as follows:

Weight of whole mixed precipitate,	= 0.607	grms.
" " crucible with contents,	= 7.025	"
" " " without "	= 6.705	"
" " bromide and chloride of silver	= 0.320	"
First weighing after passing over the chlorine	= 7.020	"
" loss of weight,	= 0.005	"
Second weighing after continuation of same process,	= 7.012	"
" loss of weight,	= .013	"
Third weighing,	= 6.991	"
" loss,	= .034	"

* Quantitative Chem. Anal. Fresenius, by Bullock & Vacher, p. 446.

Fourth weighing, ... = 6.965 grms.
" loss, ... = .060 "

Fifth weighing, ... = 7.025 "
" loss, ... = .062 "

Sixth weight and loss the same. Then using the rules of proportion above stated—

44.54 : 80 = .060 : × = .111 grm. or bromine in crucible.
320:607 = .111 : × = .211 grm. or bromine in the whole amount of precipitate.
80:119.11 = .211 : × = .314 grm. bromide of potassium.

Thus of .350 of a gramme dissolved in urine
.314 " " was recovered.

.036 lost by impure chemicals and an insufficient laboratory.

This was the result of our first quantitative analysis for bromide of potassium, and the process is given in detail to show that all ordinary caution was exercised that could occur to our minds.*

The details of the analyses to be hereafter mentioned will not be transcribed.

M. Rabuteau mentions in a recent publication,† that having tested the urine for two months, and having found a salt of bromine each time, and this when only one gramme had been given, was so much surprised, that he obtained some urine from a person who had not been taking a salt of bromine, and still found a trace of bromine present by the qualitative test before mentioned. In seeking for an explana-

* In these analyses the ordinary commercial nitrate of silver (lunar caustic) was used, which may be the cause of our not obtaining more accurate results. This would not, however, interfere with the *relative* results, which are the main points to be considered.

† Gazette Hebdomadaire, 1868.

tion of this phenomenon he ascertained, if a quantity of urine exceeding one hundred and fifty grammes (℥ vj.+)* was employed he almost invariably detected some bromine. In any less quantity no bromine was perceptible in ordinary urine. Therefore he is disposed to add this metalloid to Bernard's list† of fourteen simple bodies found in man and the higher order of animals.

CHAPTER III.

EFFECTS UPON THE SECRETIONS.

We will now consider the effects of bromide of potassium upon the secretions. The quantity of the saliva does not appear to be modified in any degree. This drug is absorbed to a very great extent by this secretion, and can be detected for twenty days‡ after one gramme has been taken. Several times have we detected its presence in the saliva within a very few minutes after its administration, and have proved its presence for a long time afterwards, almost as long as it is present in the urine. Voisin states that this drug appears very early in the saliva, and remains there as long as it can be detected in the urine. His statements are confirmed by some experiments of Rabuteau, before alluded to; and, as I have not found any cause to doubt these observers, the details of my experiments have not been given. There seems to be no chemical decomposition with the gastric juice.

* We never employed in our analyses more than one hundred grammes at any one time.

† Cl. Bernard—Sur les substances toxique et medicamenteuses. Paris. 1867. Page 40.

‡ Gazette Hebdomadaire, 1868, p. 582.

When pure, it at first *may* stimulate the mucous membrane to throw out its mucus; but, after one or two days use, its tendency is to dry up this secretion, mouth and fauces, and especially by the excreta of the intestinal canal, which, with a few exceptions, are dry, hard, and infrequent.

Excretions.—With regard to its effect upon the kidneys there is much debate. Does it or does it not produce diuresis? It is very difficult to judge of this effect, from various reasons, which are evident to every one. The quantity of urine passed in twenty-four hours varies in different persons, and in the same person at different times. The state of the weather, of the skin, of the general health, diarrhœa, constipation, quantity and fluidity of blood, all show their effect upon the urinary secretion, as is shown by a dryness of the mouth and fauces, and especially by the excreta of the intestinal canal, which, with a few exceptions, are dry, hard, and infrequent. Therefore, it is almost impossible to place an individual constantly in the same relations. This may explain some of the inconsistent results determined by various experimenters.*

If it does augment this excretion, it is probably due to the change of blood tension in the kidneys, on which Bernard has found that the activity of kidney secretion in part depends.†

Its effect upon the intestine, it has been stated, seems to be rather constipating, and may be thus explained: by a diminished secretion from the mucous surface, and by a diminution of the reflex sensibility and of the muscular contractility. This is shown by its effect upon the pharynx and all the external portions of the mucous membrane. That this effect is not caused by the immediate contact of the drug

* Gazette Hebdomadaire, 1868, p. 582. Damourette and Pelvet, Bull. Gen. de Ther., vol. lxiii. p. 296.

† Liquides de l'Organisme, Baillière et fils, t. 2, p. 155.

may be known from the fact that the injection of a weak or a strong solution of this salt into the rectum will create a violent irritation of, and discharge from, the bowel.

I know of two cases of chronic constipation relieved by a dose of the bromide, and where have been taken large doses of the ordinary cathartics without producing an intestinal discharge; in other instances one or two doses of the bromide have caused an evacuation of the bowels. These fæces, carefully and repeatedly analyzed, give no indication of the presence of a bromide.

In such cases the effect of the drug seems to be exerted upon the muscular fibres, inducing their contraction and thus causing an excessive peristalsis, from which there results, sometimes, a violent expulsion of the fæces.

Other cases have been *recorded* where this hypercatharsis was so marked, that the drug was discontinued.

Out of thirty-seven cases treated for epilepsy by this drug,* two patients had to discontinue its use, because catharsis was produced. These cases are, however, very rare, and we are disposed to place them all under the same conditions.

The excretion from the pulmonary mucous membrane, after the continued use of this drug (that is, when the system is under its influence), is diminished, and if the influence is maintained, a dry and annoying cough may be induced.† Hoarseness, aphonia, dry cough, laryngeal pain, sub-crepitant râles,‡ all point to this effect.

The difficulty of expiration,§ oppression, &c., would tend to show a loss of muscular contractility in the pulmonary tissue. If, however, the drug is impure, as it is sometimes combined with the iodide of potassium, opposite results may

* Williams, abstract in Boston Med. and Surg. Journal, lxxi. p. 422.
† Haneau, Gaz. Heb., 1868.
‡ Voisin, Bull. Generale de Therapeutique, lxxi. p. 101.
§ Ibid. p. 102.

take place, that is, a catarrhal affection of the mucous surfaces.

That bromide of potassium often has iodide mixed with it, has been noticed by Dr. Garrod* some twenty years ago, and there are a few American preparations which also contain this impurity at the present time.

CHAPTER IV.

ELIMINATION.

We will next consider the elimination of this drug from the system, its ways and conditions, before viewing its action upon the economy. Voisin† has considered that, as the breath smells strongly of bromine after the continued use of bromide of potassium, it may be partially eliminated in this way. If this is a fact, then this salt must be decomposed, and the bromine, being volatile, may escape. We find a bromide in the saliva, urine, and sweat, and in each of these a large amount of potash.

Exp. X.—We find that three different persons exhaling for fifteen minutes, after a continued use of bromide of potassium, through glass into a test tube filled with water and bisulphide of carbon, do not produce the yellow color of bromine. On adding a few drops of strong chlorine water, the bisulphide does not change its color. Therefore, we conclude that bromide of potassium is not decomposed nor eliminated by the breath. The peculiar smell this eminent experimenter distinguished, we think no other than that produced by other salts of potassium, such as the chlorate of

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* Medical Times and Gazette.
† Op. cit.

potassa and the iodide of potassium. As this drug, passing through the mouth, mingles with the saliva, and the mucus from the mouth, pharynx, and nose, there could not be any use in analyzing the excretions from the mucous surface of the lungs.

I do not consider that the saliva assists in the elimination of any drug, as, unless accidentally expelled, it passes into the stomach and is again absorbed into the economy. I have already mentioned the ease and rapidity of the absorption of this drug by this secretion.

That bromide of potassium is expelled with the urine has been noticed by Voisin, Damourette and Pelvet, in the Bulletin Générale de Thérapeutique, and by many other observers. My experiments and observations have been made with the particular view of determining under what conditions this occurs, and if certain conclusions be here mentioned which are not altogether new, it may be pardoned, from the fact that the results arrived at are independent of others, because the before mentioned chemical process* has not been carried out by any of the above writers. Great care and much time have been devoted to this subject, and the results, it is hoped, may be of practical value.

It has been already stated that M. Rabuteau has found bromine in normal urine. This, however, only could be found in a quantity much exceeding one hundred and fifty grammes. It would be proper to state that at no time did we use so large a quantity as this in our analysis. This observer states that he has found for twenty days traces of a bromide in the urine of a person who had taken one gramme (grs. xv.) only of this salt, and that traces could also be found in the saliva of the same person during the same period.

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* Vide p. 14.

In our experiments we could only find traces at the end of forty-eight to fifty-two hours after a single dose. If, however, the dose was continued for a few days, the presence of a bromide was apparent for a much longer time, varying with the amount taken and the time the exhibition of the drug was continued. The results of the experiments of M. Voisin* must be doubted, if M. Rabuteau is correct; his idea being that there is a small quantity of bromine present in normal urine; for in their chemical analysis, 325, 400 and 1,000 grammes of urine were used; and the quantity of pure bromide of potassium crystals varied considerably in each analysis. From the 400 grammes, .40 were obtained; from 1,000 grammes, .095; and from 850 grammes, 3.75 grammes. Their method of analysis is not related.

We always, during the first forty hours after an ordinary dose, found distinct signs of the presence of a bromide. The experiments were repeated very often and the same result was obtained.

Exp. XI.—During twenty hours, fifty grains of bromide of potassium were taken in five different doses. The urine passed during the first twenty-four hours was preserved, and amounted to fifty-one ounces. Of this about two ounces was analyzed for the quantity of bromide eliminated by the kidneys; from this amount a little more than one grain, and, by calculation, from the whole fifty-one ounces $28\frac{72}{100}$ grains were recovered. Thus more than one half the amount of bromide of potassium was eliminated during twenty-four hours after the first dose was taken.

Another experiment was undertaken for the purpose of finding how much of the drug was eliminated during the second twenty-four hours after a dose of the drug whose action we are considering.

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* Op. cit.

Exp. XII.—Ten grains were taken, and, of the thirty ounces of urine passed during the second twenty-four hours, two ounces were carefully analyzed, and, by our process and calculations before mentioned, there was recovered about three and three quarters grains. Thus a third of this salt is eliminated during the second twenty-four hours.

We think that these, combined with other experiments for qualitative analyses for a bromide, would show, that—

Prop. B.—Bromide of potassium is largely and mainly eliminated with the urine by the kidneys, and that during the first day the largest quantity is eliminated, and less during the second day, and so on till there is none left in the system.

Several times were the fæces analyzed and tested for the presence of a bromide, but always with a negative result. A large amount of caustic soda was added before each analysis to allow any free bromine, which might have been volatilized during the ignition of organic matters, to combine in the formation of bromide of sodium. We are forced to conclude either that our chemical process in itself was deficient, or that bromide of potassium is not eliminated with the fæces. In some subsequent investigations for the action of bromide of ammonium, the fæces were carefully collected and analyzed by two members of my class, and no trace of a bromide could be detected. Considering that so large an amount of the salt is eliminated by other organs and the easy absorption by the mucous membrane, it is fair to suppose that, ordinarily, the bromide of potassium, when given in small doses, does not pass through the intestinal canal, but is absorbed before it can mingle with the effete contents of the bowels.

M. Voisin considered that because an eruption of the skin occurred after the continued use of this drug, this organ assisted in its elimination. Acne may be produced from the action of this drug; but why may it not be caused by the

altered condition of the capillary circulation, and thus inducing those inflammatory conditions of the skin, due to an obstruction of the circulation? Indeed M. Hardy in his lectures (sur les maladies cutanées accidentelles) considers this condition of the circulation an important and often neglected cause of acne. As we shall endeavor to show hereafter, bromide of potassium does produce this very effect upon the capillary circulation. To show that this salt is eliminated by the skin, the following experiment was tried, and repeated twice with a similar result.

Exp. XIII.—In the first, forty grains of the drug were taken in two doses three hours apart. Immediately after the second dose I entered a hot-air, commonly called a Turkish, bath, and remained in it one hour, and during that time collected four ounces and a half of perspiration. By a careful analysis, there was found contained a little more than one third of a grain of bromide of potassium in this amount of sweat. It may be remarked that this amount of excretion from the skin was abnormal; but, by the researches of Valentin, the daily amount of sweat is about $1\frac{3}{4}$ pounds, or ℥ xlii. According to approximate calculation, about three grs. might have been eliminated in twenty-four hours through the skin.

This, confirmed by repetition at other times, proves that the skin assists in the elimination of this drug; and moreover we are able by—

Exp. XIV.—To determine whether during the *second* day the elimination by the skin continues; five ounces of sweat were collected in a hot-air bath, entered thirty hours after a dose of eighteen grs. of bromide of potassium. This sweat, treated in the usual manner, showed the presence of a large amount of a bromide.

We may then conclude that—

PROP. C.—The skin assists in the elimination of this drug from the system during the second day as well as the first.

Summary of the means of elimination:—

Of the various organs which carry off the effete matters of the human economy, two only eliminate this drug, viz., the skin and urine. In the exhalations from the lungs and the contents of the rectum, we cannot find any evidence of this drug.

CHAPTER V.

EFFECTS ON THE BLOODVESSELS.

WHEN applied in a state of solution to the interdigital membrane of one posterior extremity of a frog, the web of whose other foot is observed through a microscope, the circulation in the arterioles is seen to be hurried, and the venules become filled with blood of a lighter shade than is generally observed. Soon, the circulation grows slower in the arterioles and the calibre of these vessels diminishes, and the whole capillary system loses its supply of blood, whilst there is less than before in the vênules and arterioles. This is probably the result of stimulation, which can otherwise be determined by the muscular contractions observed throughout the trunk and limbs.

Half an hour or more after this, when the animal has become calm, the blood returns to the capillary system in rather larger amount than before; and in a little while the constriction or tetanus of the arterioles is noticed, which continues some time. The blood in the venules diminishes and approaches more to the color of that in the arterioles.* If

* While making these investigations, I attempted some observations on the circulation in the crania of a frog. During the manipulation some bloodvessels

the muscular tissue be now observed without the aid of a lens, it will be found to be pale and exsanguine, which is due to this modification in the supply of blood to the capillary system. This same pallor of skin has been noticed by Voisin in his patients who have been for some time under the influence of bromide of potassium. Can it be that this drug affects the nerves in somewhat the same way that has been observed in chlorosis, interfering with assimilation, and depriving the blood of its proper allowance of red corpuscles? Fortunately, if this theory is correct, the interference is only a temporary one, for the nerves soon after must recover their power, or some serious constitutional trouble would ensue.

Meuriot explains the action of this drug upon the circulation, as compared with atropine, in the following words, which I translate: "It is seen that bromide of potassium acts much more energetically upon the contractility of the vessels than atropine. * * * * The bromide of potassium exaggerates the arterial tonicity, tetanizes the arterioles, slackens or arrests the circulation, and produces an oligæmia of the tissues."*

Some experiments have been undertaken in Berlin, by which it has been proved in a satisfactory manner that upon frogs the sedative action of this drug is upon the vaso-motory nervous system, a translation of which I will give you:

Two frogs were selected, as nearly as possible of the same

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were severed, and the field of vision became afloat with blood corpuscles. The addition of the solution of bromide of potassium changed their color to a peculiar rose red. This occasioned some surprise, but was supposed as something, perhaps, accidental, though unaccountable. However, on reading a memoir by M. Meuriot, I find this same observation with regard to the color produced by the bromide of potassium. This bright red color is probably due to an excess of arterial over venous blood in the capillary system; and as the tissue around is pale, this color is remarkable.

* L'Etude de la Belladonne, Paris, 1868, p. 50.

size; one was used to correct the experiment. The other was poisoned.

FROG NOT POISONED.

The metronome was regulated to 100 vibrations per minute. The legs of the animal were loosely bound together in the middle with soft woollen cords, which would not compress the limbs. A vessel of a given size and with an estimated quantity of distilled water was placed under the feet; then quickly and, at once, all six toes of both feet were cut off at the same height. The time, during which the observation was carried on, was two minutes, or 200 vibrations of the metronome.

The blood, flowing by drops, from each foot was counted, and received into the vessel. (The binding together of the legs being easy had no influence on the value of the *experiment*.)

Number of drops falling into the vessel:

Right leg.		*Left leg.*
1		2
1		1
1		1
1	in two minutes.	1
2		2
1		1
1		1
8		9

FROG POISONED.

(This frog before poisoning drew his foot out of the sulphuric acid mixture, after nine beats of the metronome).

Waiting till the reflex power in the left leg had sunk to thirty, and in the right to forty-five beats; then all six toes of both feet were cut off at the same level.

In two minutes only two drops exuded from the right leg.

The left plexus ischiadicus was then divided.

In two minutes ten drops of blood flowed from the left leg.

This is a very valuable experiment, the results of which were confirmed by repetition; and shows conclusively, in another way, that the action of this drug is through the vasomotor nerves upon the bloodvessels.

CHAPTER VI.

EFFECTS ON THE NERVOUS SYSTEM.

It might be supposed, from what has been said, that the nerve cells have been impaired by the action of this drug, and that the conductibility of nervous impressions has been interfered with. Nerves from animals poisoned by this drug will convey an electrical current, and electricity will pass through a strong solution, or even through the solid salts of bromide of potassium, isolated in a glass tube, without any diminution of the electric current. The retardation of the circulation must have some dependence upon the reflex nervous system, and we shall soon see that this drug has a decided effect upon this system.

M. Laborde* made some experiments to determine this question, which are well worthy of examination.

He, at first, causes a frog to absorb by the interdigital membrane three centigrammes of this drug. The animal immediately moves spontaneously after the poison is absorbed. Then he remains quiet, but withdraws the extremity if irritated by pinching, pricking, or galvanism. This response ceases in twenty minutes, in the posterior extremities first, and then in the anterior. In another experiment with the same dose the heart pulsates after cessation of responsive action (for two hours). In several of these experiments with this same dose, he reports that a state of tetanism occurred in eight to ten minutes after the absorption of the poison, lasting two minutes, and was then succeeded by a collapse. Also that at first the muscular fibres contract, afterwards are in a state of relaxation, and will not contract by stimulation.

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* Archives de Physiologie, 1868, p. 422.

Now these phenomena all point to the same effect as that noticed in the circulation: overstimulation of the power of contractility, soon followed by a state of relaxation or collapse.

To what may this be due? To the direct contact of the salt with the tissue? We have seen that almost immediately a large portion of this drug is absorbed and carried by the blood through the various organs and tissues. We have seen no cause to suppose the decomposition of this salt, but that it is bromide of potassium in the blood, and in the urine and the sweat.

An experiment was suggested to me by this thought.

Exp. XV.—Both of the sciatic nerves of a frog were exposed and were isolated by glass rods. Galvanism caused an equal amount of contraction in both limbs. A sponge was then saturated with distilled water and placed on the right sciatic nerve, and another sponge was saturated with a solution of bromide of potassium (ʒ j. = grs. xiij.) and placed on the left nerve. The galvanic current was then applied to each in turn. The right foot responded to the stimulation. The left foot did not respond to the stimulation. The left was then thoroughly washed with distilled water from a wash-bottle, and then the galvanism applied. The left foot now responded; the bromide sponge was again applied, and the response ceased. The nerve and tissues were again washed and the bromide sponge was applied to the right nerve, the water sponge to the left. The left foot contracted by the stimulation. The right foot did not contract by the stimulation.

This experiment was repeated several times with a similar result, the bromide sponge always preventing transmissibility of the shock through the nerve, while the other, water sponge, did not. These sponges were then applied to the brachial plexus of each side, the nerves being isolated on

glass rods. The poles of the battery were applied one on the nerve, the other on the extremity. The same result followed the application.

This experiment did not hold good with other animals, such as dogs and rabbits, in all of which the transmission of electric current was not prevented by the saturated solution of the drug. An explanation is suggested that the irritation of the drug may in some way have caused a partial anæsthesia of the nerve operated upon.

M. Pelvet,* in speaking of this drug, says that it successively attacks the properties of the sensitive and motor nerves, the brain, cord, medulla, and the muscles. The contractility of the heart outlives every other organ. Respiration is indirectly affected.

Eulenberg and Guttmann† say that two to four grammes (ʒ ss. — ʒ j.) injected hypodermically into rabbits kill them in ten minutes, with signs of paralysis of the heart. Internal administration had the same effect. Sensibility and the power of voluntary movement were diminished. They observed always a corrosion of the mucous membrane of the stomach and infiltration of blood. In smaller doses they noticed quiverings in the muscles.

They considered that this acted like other salts of potassium, and presented nothing characteristic of bromine. Pure bromine injected in much larger quantities had no such effects, and did not cause death.

On the contrary, M. Laborde considers that bromide of potassium is the only drug that produces this peculiar action. Bromide of sodium and potassium had an entirely different effect, even when the latter caused death.

With this last observer I am more disposed to coincide, for his experiments were made with much care and ingenuity,

* Gazette Hebdomadaire, Dec. 6th, 1867.
† Idem, July 5th, 1867.

and more clearly illustrate his views. He states that potassium exalts the power of motility. He endeavors to show, by a very interesting experiment, that bromide of potassium does not destroy the volition, but affects the spinal cord and reflex system only.

A frog is decapitated and laid on the table; to another he caused the absorption of twenty-five centigrammes (four grs. or less). The first loses the sense of reflex power by stimulation, and afterwards exhibits the usual symptoms of tetanus, &c. The frog who had been beheaded has shown no loss of reflex action, but is now caused to absorb the same dose of this drug. The absorption occupies a longer time, but when it is accomplished, this animal also loses reflex response to irritation, and is soon in the same condition as the first frog. From this M. Laborde concludes that bromide of potassium produces paralysis of reflex action, and has nothing whatever dependent upon the volition of the animal experimented upon. In Eulenberg and Guttman's experiments, it may be noticed that they supposed paralysis of voluntary movement in warm-blooded animals. This, however, would be difficult to determine from paralysis of the sensitive nerves; and, as M. Laborde* by his experiments on frogs would show, that not only was there voluntary movement in one or two of these experiments, but that, in the two decapitated frogs (in which volition was put in abeyance), the power of reflex action was not lost until the absorption of the drug; and, as we know that this reflex action is very persistent and of long continuance in beheaded frogs, is it not possible that MM. Eulenberg and Guttman confounded the absence of volition with the loss of reflex action?

PROP. D.—The loss of reflex action is due to anæsthesia induced by the deprivation of blood from the peripheral

* Op. cit. p. 423.

nervous extremities, and, also, from the central nervous system, this last occurring after the first. Thus we may get loss of sensation first and then paralysis of reflex action. This is not strange if we compare the syncope produced by excessive hæmorrhage, in which there is anæsthesia and loss of reflex action.

That sedation of the heart's action is, in part, caused by the obstruction to the circulation in the smaller arteries and capillaries, from reduction of their calibre, is evident. This is a physiological law laid down by Marey.* But, probably, the same influence which the drug exerts upon the muscular contractility of the arteries, would eventually enervate the cardiac pulsations.

The first effect produced by a moderate dose is acceleration of the pulse, which in an hour is succeeded by a retardation and diminished impulse. Thus, this drug has been recommended in nervous irritability of the heart where there is hypertrophied muscular tissue from disease of the mitral valve.† Eulenberg and Guttman showed its local action upon the heart, which they thought caused paralysis of that organ. In a large dose applied locally this would very naturally happen, but when administered at a distance slowly received into the circulation a less amount would produce the physiological action peculiar to the drug, without producing paralysis of the heart. In large, or very poisonous doses, Laborde noticed that frogs died very rapidly in a state of muscular relaxation. In moderate doses producing the poisonous action more slowly, the period of tetanism of the muscles occurred first, and subsequent relaxation and death, in which the muscles remain relaxed for some time.‡

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* De la Circulation du Sang, Paris, p. 307.

† Stillé, Mat. Med. and Therapeutics.

‡ This apparent difference may be understood, if we consider, that an overdose would not allow the bloodvessels to contract and to pass through the suc-

We have seen by direct experiment, that when applied to the muscular substance in solution, or in a solid form, and electricity is applied, the muscular fibres contract both in frogs and warm-blooded animals. Therefore, this drug does not put in abeyance muscular contractility. M. Laborde,* however, observes that the peripheral extremities of a nerve in a frog under the action of this drug, separated from its central portion by a ligature, conveys electricity and produces contractions in the limb; but the central portion (above the ligature), stimulated by electricity, does not produce contractions in this limb. From this he infers that the action of this drug is upon the spinal cord, and not upon the extremities of the nerves; in other words, he would conclude that in a frog, also other animals and even man, bromide of potassium puts in abeyance the reflex functions of the spinal axis, and that afterwards the extremities of the nerves lose their vitality, and, lastly, the muscular fibres their power of contractility. Now following out this theory upon the action of the heart, we would suppose the same phenomena of action, viz.: That the nerve (par vagum perhaps) is paralyzed by the drug in the ordinary sequence, that is, after the nervous centre has lost its vitality, and that the muscular contractility is preserved, keeping up the cardiac pulsations for a longer or shorter time afterwards. This would seem a very plausible method of explanation; but then, we must not lose sight of the fact that Eulenberg and Guttman, in large doses injected near the region of the

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ceeding steps that we have endeavored to point out in the observations on the capillary circulation. In this case, the vessels are paralyzed and the blood becomes stagnant, thus producing congestion where a therapeutical dose produces *oligæmia*. Congestion in the brain would cause the stupidity and torpor which occurs. There is the same harmony of action upon the bloodvessels and the muscular fibre: where we have tetanus of the former we have tetanus of the latter; relaxation of the former, relaxation of the latter.

* Op. cit., p. 439—Exp. VII.

heart, produced paralysis of this organ. Was this caused by enervation of the nerve, commencing at its central portion, or by destruction of the muscular contractility? If both of the pneumogastric nerves are severed, the animal may live a few hours with great impediment of circulation and respiration, and finally die in a state of exhaustion. Taking into consideration this fact, and that muscular contractility persists after death, we should infer that paralysis of the nerves which regulate the heart's action occurred. Now in frogs the power of muscular contractility is very active and persistent, much more so than in any warm-blooded animals.* Laborde's observations were founded on experiments performed on this animal only, and, therefore, must be accepted with due caution in regard to the action of this drug on the warm-blooded animals, and especially on man, in whom the nervous system is arranged with so much more perfection, and so much more widely distributed, and the functions more subdivided. In all the experiments which I have observed on warm-blooded animals the cardiac pulsations ceased within a few minutes after the signs of respiration. Electrical stimulation produced muscular contractions, whether applied to voluntary or involuntary muscles, to nerves either peripheral or central.

PROP. E.—The action of bromide of potassium on the nervous system may be explained by its action on the capillary, arterial or central circulation; it modifies reflex action, by over stimulation and subsequent paralysis of the vasomotor system, thus producing oligæmia of the tissues and nerve substances, depriving the latter of the vitalizing pro-

* We know that cardiac nerve-ganglia maintain their vitality and the cardiac pulsations continue even after the heart is separated from the body; and the ventricle will beat even when separated from the auricle and other ventricle *in frogs*. Likewise respiration in frogs is maintained by the skin, as has been before mentioned.

perties of the blood. *There is no alteration of the nerve substance or cells.*

In what other way can be the explanation of the efficacy of this drug in certain forms of epilepsy, accompanied by a capillary injection of brain or spinal axis, or in hysterical epilepsy where the cause is exaggerated reflex sensibility? Bromide of potassium, though the most certain of all remedies to reduce the number of epileptiform convulsions in certain cases, *never* produces a permanent relief. As soon as the remedy is discontinued the convulsions recur, and in the same manner as before.

The efficacy of belladonna may be explained in the same manner, though the action of this drug* on the capillary circulation is perfectly distinct from that of bromide of potassium.

We would repeat, then, that the action of this drug is perfectly explicable, if we take into consideration merely its action upon the circulation, that the modifications of reflex sensibility may be due to the same cause. If the circulation in a limb is temporarily or permanently arrested by disease or ligature, that limb loses reflex action, and, likewise, sensibility. Is it necessary to lay the blame upon the spinal axis? But it may be said that this method of reasoning does not explain the primary excitement caused by this drug. It most certainly does; for we have always an excitement of the circulation both capillary and central, when this drug is first received into the economy, and then a subsequent sedation of the circulation.

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* Vide Boston Medical and Surgical Journal, March 11, 1869.

CHAPTER VII.

CONCLUSIONS.

I.—Bromide of potassium is easily absorbed by the mucous membrane wherever they are placed in contact.

II.—This drug is *easily* absorbed by the skin, provided the water in which it is dissolved is below the temperature of 75°F. If the temperature is above 96°F. it is not absorbed.

III.—The elimination is conducted by the skin and kidneys; as the saliva is a secretion, its presence in this fluid is not a proof of its elimination.

IV.—In therapeutical doses bromide of potassium is not eliminated by the intestines or lungs.

V.—Bromide of potassium passes out of the system without decomposition. As most of the chemical transformation of drugs takes place, according to Bernard, in the laboratory of the kidneys, Dr. Bill's theory in regard to the interchange between chlorine and bromine in the blood, probably, is erroneous. If there is an interchange, it is in the kidneys, or outside of the body (in other words) that the transformation must occur.

VI.—The effects of the drug are produced by its direct action upon the bloodvessels or the vaso-motor system which control the contraction of these vessels, which explanation may account for all the physiological or therapeutical conditions brought about by the exhibition of this drug.

VII.—There is probably no different or opposing action in proportion to the dose administered, which cannot be said of all drugs. The larger the dose the more intense and the longer the action upon the vaso-motor system.

VIII.—Its action upon the general nervous system is secondary and dependent upon that of the vaso-motor nerves.

That it affects certain parts where there may be a determination of blood is not contrary to the known laws of physiology. Lack of healthy resistance to disturbing influences allows the bloodvessels to be dilated, and, consequently, surcharged; the presence of this drug stirs up the opposing influence which contracts these vessels. This influence would be exerted upon the diseased portion of the system more powerfully than upon the healthy portion.

IX.—Bromide of ammonium, in *almost* every respect, has the same action as bromide of potassium. This, I judge, from the results of more than twenty experiments conducted this last winter with a class at my laboratory (which are herewith appended).

Exp. XVI.—A guinea pig.

At 0 0′ 0″.—4.30 grammes (sixty-one grains about) of bromide of potassium in solution, dissolved in ʒ vj. of water, was injected by means of an œsophagean tube into the stomach.

0 5′ 0″.—Respiration 108 and regular, though inclined towards spasmodic; circulation very rapid.

0 15′ 0″.—Temperature (rectal) 34.8′ (C.);* the animal is sluggish, though sensibility is still preserved.

0 20′ 0″—Pulse about 60, and from this time increased in rapidity though it decreased in force.

0 25′ 0″.—Death, preceded for a few minutes by gasping and spasmodic respiration. Heart ceased beating within a very short time of the cessation of respiration.

Autopsy—immediately after death.—Trachea and œsophagus uninjured. The heart contracts by stimulation. The stomach was finely injected on the external surface, though pale on the internal surface, with here and there a few dark-colored (hæmorrhagic) spots, at which the mucous is easily

* Normal rectal temperature in this animal is thirty-eight (C.).

separated from the submucous cellular tissue. The brain substance and spinal cord were pale. The membranes at base of the brain and around the spinal cord were injected with venous blood.

Exp. XVII.—Forty-five grains of bromide of ammonium in half an ounce of water were injected, in the same manner as above, into the stomach of a guinea pig.

3′.—The rectal temperature was 38° Cent.

5′.—The respiration became jerky—125 to the minute.

10′.—Cardiac pulsations 108. The animal seemed stupid, but sensibility to irritation preserved; unable to walk; lay on its belly, with the legs extended helplessly behind it.

13′.—Gasped for breath; rectal temp. 36.5° Cent. On pinching in the vicinity of the brachial plexus, or the crural, clonic convulsions were produced, speedily becoming tonic, with marked opisthotonos, and in this state the animal—

28′.—Died, and the muscular spasms were relaxed. At the moment of death the fæces and seminal fluid or mucus (a gelatinous cylindrical mass) were ejected.

Autopsy—fifteen minutes after. Heart and muscles contracted to electric stimulation. Stomach, had the same vascular injection as in Exp. XVI. on its external surface. The contents were squeezed out, and the cavity, blown up with air, was dried, varnished, and is still in our possession. The veins of the cerebral membrane were injected, as well as the venous sinuses at the base. Lungs normal, float on water. Heart normal.

Exp. XVIII.— ʒ ij. of bromide of ammonium in ʒ iij. of water were placed in the stomach of a large-sized healthy rabbit.

3′.—Began to show signs of drowsiness, stopping in his jumps and letting his head fall over to one side; sensibility unaffected. Expelled some fæces.

7′.—Pulse 400.

9′.—Falls on to his belly, all extremities extended; sensibility heightened, starts at a sudden sound or touch; head turned to one side.

14′.—Was taken up by the ears, which was followed by clonic convulsions, accompanied with cries; pupil is dilated; lay quiet upon the floor. Cardiac pulsation 80, irregular; spasmodic muscular contractions, of face and forelegs.

23′.—Another cry, followed by convulsions. Sensibility to touch subsided.

28′.—Another slight convulsion, followed by muscular relaxation and death.

Autopsy.—On opening the skull a gush of dark venous blood came out; capillaries not injected and consequently could not be distinguished; brain substance pale, cerebellum as well as the hemispheres; veins at the base of the skull injected; a clot in pia mater of middle lobe of hemispheres; on either side of the choroid plexus were clots, the plexus itself being distended; a clot in left lateral ventricle almost filling it; lungs floated on water; little urine in bladder; none had been injected from commencement of the administration of the drug. Grs. vi. $\frac{3}{10}$ of bromide of ammonium was collected from the contents of the stomach.

Exp. XIX.—A piece of the skull of a rabbit ($\frac{3}{4}$ of an inch x $\frac{1}{2}$ an inch) was carefully removed, exposing parts of both hemispheres. Ten minutes after the operation, grs. x. of the same salt dissolved in water was placed into the stomach through an œsophagean tube. The bloodvessels of the membrane, covering the exposed surface of the brain, were plainly visible to the naked eye or through a lens, and were filled with dark blood.

Seven minutes after, a contraction of the vessels and a shrinking of the brain substance were plainly apparent. Ten minutes after, the color of the blood gradually changed to a peculiar light red (rose red).

45 min. Capillary injection and expansion of the brain substance; animal is quiet, and the capillary injection is less marked. Slight muscular spasms along the muscles of the back. The brain resumes its natural prominence, then becomes slightly shrunk; and the capillary injection entirely disappears, leaving the brain pale. Two drops of a strong solution of the same salt is applied to the brain; a few minutes after, the capillary injection, caused by the application, is succeeded by anæmia, in which the veins are injected, the capillaries empty, and the brain substance expanded. This is soon succeeded by the same effects as noted above, and the brain remains pale and shrunken; in a state of oligæmia, in which the veins as well as the other vessels are diminished in calibre and devoid of blood. The animal was then killed, as there was no time for further observation. The urine showed the presence of bromine.

Exp. XX.—The nerves of a frog's leg were dissected out as high up as the lumbar vertebræ, and soaked in a strong solution of bromide of ammonium; electricity, applied above and below, caused muscular contractions in the limb. The central end of the nerve was cut off at the spinal cord. The nerve of the other leg treated in the same manner caused the same result.

Exp. XXI.—The soft parts and bone of a frog's thighs were cut off, leaving the sciatic nerves untouched. The nerves were immersed in a bath of a saturated solution of bromide of ammonium, the extremities emerging upon one side of the bath and the trunk upon the opposite side. The poles of the electric battery were applied to different parts of the trunk and to the extremities. The current was transmitted, in every case, producing muscular contractions in the trunk and limbs. One nerve was then divided, and the poles were applied upon the trunk and upon the cut nerve in such a way that the fluid conducted though feebly the electric current.

Exp. XXII.—Perspiration collected during a Turkish bath, without any of the drug being taken, gave no sign of a bromide on analysis.

Exp. XXIII.— ʒ iij. of urine collected during twelve hours after a rectal injection of bromide of ammonium, grs. xx. in beef-tea, showed the presence of a bromide.

Exp. XXIV.— ʒ j. of gastric juice containing bromide of ammonium grs. x., treated without caustic soda and then tested, indicated the presence of a bromide.

Exp. XXV.—Grs. x. of bromide of ammonium were given in a piece of meat to a dog with gastric fistula; seven minutes after, ʒ j.+ of the contents of the stomach were drawn off, which, twice carefully analyzed, indicated no trace of bromine.

Exp. XXVI.—Less than a grain of the bromide of ammonium, placed upon the web of a frog's foot, caused, in the other foot, observed under the microscope: 1st, a contraction of the arterioles and venules; 2d, dilatation of the artery only; contraction of the venules persists.

10 minutes after the application—

3d, the arterial pulsations remain about the same in force and frequency; the arteriole is contracted to half its first capacity; current moves more slowly.

Exp. XXVII.—Grs. ij. of bromide of ammonium were placed upon the web of a frog's foot, and the other foot placed under the microscope.

In 20 minutes the arteriole became contracted as above. The pulsations in the arterioles gradually decrease, and the blood from the venules is received into the larger veins, which after a while in turn become emptied, thus producing what is called oligæmia, or exsanguineous tissue. In all these cases observed, when there was struggling the circulation moved more rapidly, and the bloodvessels were filled with more blood.

Exp. XXVIII.—One of the students in my class took at 7, P.M., grs. xl. of bromide of ammonium in ʒ j. of water. Went to bed at 10.30, having noticed only a slight excitement of the circulation, flushing of the face, prickling sensation in the skin and tightness at the temples.

At 2.45, P.M., on the next day, took a rectal injection of grs. xl. in some mucilage of starch.

In 45 minutes experienced the same excitement of the circulation as noticed above, besides feeling a slight nervous excitement, such as he has after taking wine.

1 00′.—Pulse 81.

1 10′.—Pulse 80.

1 15′.—Pulse 81.

1 30′.—The nervous and vascular excitement subsided.

2 00′.—Felt as usual; spent the evening in jovialty and felt no sleepiness. At night, pulse 75, slept well, and had a good appetite for breakfast; dejection normal, but less in quantity. Urine, passed twenty-three hours after the last dose, gave distinct indications of the presence of bromine.

Exp. XXIX.—Another of the students took at 10, P.M., grs. xl. of bromide of ammonium in a claret glass of water, on an empty stomach. Pulse, before taking the dose, 80.

15′.—Pulse 88.

30′.—Pulse 80.

40′.—Vascular excitement, and exhilaration as after taking morphine. This gradually decreased, and was lost in a fit of drowsiness.

1 15′.—Found himself nodding, and then retired; respiration was normal; skin cool and moist.

Arose the next morning at half past six, feeling as well and bright as usual. Had a dejection during the day. Towards evening he noticed uneasiness in the bowels, and the next day decided diarrhœa set in, and lasted for twelve hours; no griping or distress was induced, except

that the abdomen felt as if distended with flatus. He never had diarrhœa, and could see no cause for this attack except from the drug.

Exp. XXX.—At 12 o'clock, before retiring to bed, the same experimenter took ammonii bromidi, grs. xx., on a full stomach. Within half an hour, felt as though he had taken a dose of opium, though less excited. Thinks that he fell asleep, without the aid of the drug; dreamed of trying to pass urine into a bottle, but could not do so on account of being constantly in a crowd of men and women.

Took the same quantity, at 5.30, A.M., on an empty stomach; collected the urine before taking the second dose, which on analysis showed the presence of a bromide.

CHAPTER VIII.

EXPLANATION OF THE ACTION OF THE DRUG.

Permit me, in a few words, to lay before you what I consider is the modus operandi of bromide of potassium, the proofs of which I have attempted to set forth in this paper.

When the drug has been received into the circulation, its action is exerted upon that branch of the vaso-motor system, which causes the contraction of the arterial vessels, thus reducing the supply of blood to all tissues, but acting, more especially, upon those which are superabundantly supplied. At first, for a short time, there may be some vascular excitement, caused by the interference with the natural conditions of the system. Within an hour, and especially after the continued use of the drug, the arterial sedation is accomplished, and may last for several hours. The central organ is also quieted, and thus we obtain a diminution of blood in the

nervous centres, as well as elsewhere, modifying the activity of their functions.

Prof. Brown-Séquard has reported some experiments in the 1st Vol. of his Journal de Physiologie, which illustrate many of the symptoms peculiar to large (but not poisonous) doses of bromide of potassium. In these experiments it is well shown that muscular irritability could be excited by the injection of red blood, even after cadaveric rigidity had ceased, and that ligature of the aorta could prevent this muscular irritability in one hour and thirty-six minutes from the time of occlusion of the artery.

I know of no authentic case of poisoning in man from bromide of potassium. I have no doubt that death could be induced, but the size of the dose must be very considerable. That much harm may be done by too indiscriminate a use there can also be no doubt, as probably a continued use of the drug will interfere with the process of assimilation. I consider its use contra-indicated in anæmia or chlorosis. That it is a specific against epilepsy is erroneous. Such cases as proceed from anæmia of the cord or any part of the brain, will be aggravated by its use. When there is congestion there will be benefit. Again, if the dose could be administered only when an attack is anticipated, it would be following out the indications of its physiological action, and in some cases this idea could be prosecuted. I shall hope in some other way to give a description of its toxicological and therapeutical relations.

CHAPTER IX.

ITS EFFECT ON WAKEFULNESS.

In order to have a full appreciation of the benefits to the generality of cases afflicted with that terrible malady, insomnia, it will be necessary to recall the cause, usually acting in such cases. Those of our readers who would prefer a full and clear understanding on the point should refresh their memory with Dr. Hammond's well known book "On Wakefulness."* I shall content myself more with the *results* of his experiments and observations. He distinguishes natural sleep from stupor and coma; in the former the natural condition of the brain is anæmic, and in the latter, venous congestion; in the latter the brain mass expands in volume, in the former it is reduced and occupies a smaller space.

The proofs of this statement he establishes beyond a doubt by experiments on lower animals, whose skull has been trephined, and by observations on certain persons whose brain has accidentally been exposed. He also cites cases where wakefulness and nightly phantasies can only be explained by this condition, and whose state becomes aggravated by the use of opiates. Also those postures, such as the supine, which determine blood to the head, aggravate, while others, such as the erect and sitting postures, ameliorate these conditions.

Again, the ingestion of easily digested food in moderate quantity determines blood from the brain to the alimentary canal, and will thus induce sleep. A slight amount of cold, such as will cause chilliness to the surface of the body and to the extremities, prevents sleep, probably by driving the

* Published by J. B. Lippincott & Co., Philadelphia.

blood to the brain.* Over-taxation of the intellectual faculties from the same effect will cause insomnia.

On the other hand, extreme cold or an immoderate meal will induce coma, from a nervous congestion of the brain, and want of aeration of the blood in circulation. This distinguished author states, also, that if in the coma produced by opium in dogs, the trachea be opened and fresh air be forced into the lungs and blood, the coma will be relieved; that in the state of chloroformization the brain is reduced in volume, and of etherization the blood becomes very dark colored, and is probably loaded with excrementitious matters, and congestion and expansion of the brain mass. Pressure on the carotids also induces sleep, and, if continued for a long time in the lower animals, will produce convulsions.

Dr. Hammond, also, states that in the dogs whose skull was trephined, bromide of potassium produced anæmia and shrinkage of the brain mass.

In cases of insomnia arising from the cerebral congestion above mentioned, great benefit has resulted from the use of bromide of potassium, so that now physicians use this drug to produce sleep and to a large extent. However valuable may be a drug in a certain class of symptoms, no sensible man should prescribe this, except where hygienic and moral treatment will fail to accomplish the same purpose. There is a tendency, it is feared, to use a new medicine, and one so especially efficacious as this, many more times than there may be a necessity for so doing. A physiological effect in the economy may be *forced* by the aid of medicine, which may be induced by gentle and natural treatment. The first should not be tried, except in certain cases evident to every practitioner, till the latter fails in relieving the symptoms. For every beneficial effect produced by physic, there general-

* In warm weather and in warm rooms there is with some people an irresistible impulse to sleep.

ly is some unnatural effect which cannot always be counterbalanced by the good.

We have seen that bromide of potassium is not eliminated very rapidly, and that the longer it is used, the more slowly does it pass out of the economy. Is there not reason, then, to be cautious in regard to its use? One case has been mentioned to us by a physician in this city, where an individual, in an Insane Asylum in our vicinity, died after the continued use of this drug prescribed by one of our most eminent physicians, and it was supposed the man's death was hastened if not actually induced by bromide of potassium.

Since writing the above, several cases have been reported, in the journals of France and of this country, of peculiar anæmic symptoms occurring after the continued use of this drug.

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